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INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

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WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY  
(PCT Rule 43bis.1)

Date of mailing  
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference  
see form PCT/ISA/220

FOR FURTHER ACTION  
See paragraph 2 below

International application No.  
PCT/IB2004/001049

International filing date (day/month/year)  
05.04.2004

Priority date (day/month/year)  
04.04.2003

International Patent Classification (IPC) or both national classification and IPC  
C07K19/00, C12N15/62

Applicant  
UNIVERSITE DE LAUSANNE

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**International application No.  
PCT/IB2004/001049

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**Box No. I Basis of the opinion**

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1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
  - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
  - a. type of material:
    - ☒ a sequence listing
    - ☐ table(s) related to the sequence listing
  - b. format of material:
    - ☒ in written format
    - ☒ in computer readable form
  - c. time of filing/furnishing:
    - ☒ contained in the international application as filed.
    - ☒ filed together with the international application in computer readable form.
    - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**International application No.  
**PCT/IB2004/001049**

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**Box No. II Priority**

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1. ☒ The following document has not been furnished:

- ☒ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).
- ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**International application No.  
PCT/B2004/001049**Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,  
☒ claims Nos. 1-44 (all partially); 25-31 (with regard to industrial applicability)

because:

- ☒ the said international application, or the said claims Nos. 25-31 (with regard to industrial applicability) relate to the following subject matter which does not require an international preliminary examination (*specify*):

**see separate sheet**

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☒ no international search report has been established for the whole application or for said claims Nos. 1-44 (all partially)
- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
- |                            |  |
|----------------------------|--|
| the written form           | <input type="checkbox"/> has not been furnished            |
|                            | <input type="checkbox"/> does not comply with the standard |
| the computer readable form | <input type="checkbox"/> has not been furnished            |
|                            | <input type="checkbox"/> does not comply with the standard |
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.
- ☐ See separate sheet for further details

**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**International application No.  
PCT/IB2004/001049

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**Box No. IV Lack of unity of invention**

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1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:
- ☒ paid additional fees.
  - ☐ paid additional fees under protest.
  - ☐ not paid additional fees.
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3
- ☐ complied with
  - ☒ not complied with for the following reasons:  
**see separate sheet**
4. Consequently, this report has been established in respect of the following parts of the international application:
- ☐ all parts.
  - ☒ the parts relating to claims Nos. 1-44 (all partially), 45 (entirely)

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**Box No. V Reasoned statement under Rule 43b/s.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

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## 1. Statement

Novelty (N)	Yes: Claims	8,9,13-16,24,26,31-34,37,38,40-45
	No: Claims	1-7,10-12,17-23,25,27-30,35,36,39
Inventive step (IS)	Yes: Claims	NONE
	No: Claims	1-45
Industrial applicability (IA)	Yes: Claims	1-24,32-45
	No: Claims	NONE

## 2. Citations and explanations

**see separate sheet**

**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING  
AUTHORITY (SEPARATE SHEET)**

International application No.

**PCT/IB2004/001049**

The document numbering corresponds to the order of citation in the search report.

**Re Item III**

1. According to Rule 66.1(e) PCT, claims relating to inventions in respect of which no International Search Report (ISR) has been established need not be the subject of international preliminary examination. Accordingly, **no preliminary examination is carried out for these claims relating to the non searched inventions (inventions 2 to 10 as identified in the ISR).**
2. Claims 25-30 are directed to methods of treatment of the human/animal body. Claim 31 is directed to a diagnostic method which could be practised on the human/animal body. Thus, claims 25-31 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

**Re Item IV. Lack of unity**

1. The application lacks unity as contravening the requirements of Rule 13 PCT. Rule 13.1 PCT states that for unity of invention to be present, all subject-matter should be linked by a single general inventive concept. Rule 13.2 PCT stipulates that where a group of inventions is claimed the requirement of unity shall be fulfilled only where there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features. **"Special" technical features** are those features that define a contribution which each of the inventions makes over the prior art.

**Eleven different (groups of) potential inventions have been recognised (see list in the ISR).** The common concept (technical relationship) linking **groups 1 to 10** together, with due consideration paid to the content of the description section, is the combination of technical features of the peptabodies of claim 1. This combination of features was known from the prior art and thus cannot define a contribution over the prior art. No "corresponding" special technical features could be identified either. Thus, there is lack of unity a posteriori among groups 1 to 10 (see reasons below in sections 2 and 4).

Furthermore, the enhancers referred to in claim 45 (**group 11**) do not have any

**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING  
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/IB2004/001049

technical feature in common with the peptabodies of any of groups 1 to 10. The fact that the enhancers of group 11 can be used in the peptabodies of groups 1 to 10 is not sufficient to establish unity. Thus, there is lack of unity a priori between group 11 and any of groups 1 to 10.

2. **D2 discloses isolated and recombinant fusion peptabodies expressed in E. coli, which bind to human epidermal growth factor receptor (hEGFR). The peptabodies of D2 comprise:**
  - (a) a portion of the human cartilage oligomer matrix polypeptide (the coiled-coil region);
  - (b) a portion of a hinge (a semirigid IG hinge region) and
  - (c) an epidermal growth factor receptor ligand (either hEGF or a biogenic insect peptide of 25 amino acids named growth blocking peptide, GBP, which possesses the ability to interact with EGFR). It is noted that hEGF is very well known to have at least a motif having a three dimensional structure (see e.g. D3, D4, or paragraph bridging pages 8 and 19 of the present application).The fusion peptabody of D2 is capable of inducing cellular death of cancer cells (see end of the results section).

**Thus, D2 discloses all technical and functional features of claim 1 of the present application.** It is noted that in D2 the fusion proteins are named either peptabody anti EGFR or Decabody. As the EGF ligand was bound to the coiled-coil region of the cartilage oligomeric matrix protein which allowed pentamerization of the EGF, and in view of the title, the fusion proteins of D2 are pentabodies.

3. In the light of the D2, the common concept linking potential inventions 1 to 10 (the subject-matter of claim 1) cannot be regarded as the "single general inventive concept" required by Rule 13 PCT because it is not novel. Therefore, there is lack of unity a posteriori for inventions 1 to 10.

Furthermore, as above stated (see section 1), the enhancers referred to in claim 45 (invention 11) do not have any technical feature in common with the subject-matter of claim 1 (common concept for inventions 1 to 10), and thus, for said invention there is lack of unity a priori.

**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING  
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/IB2004/001049

Since no other feature could be identified neither in the description nor in the claims that could be considered a "special" technical feature in the sense of Rule 13.2 PCT, **each peptabody (and the uses, methods, and kits involving said peptabody) and the enhancers (claim 45) must be regarded as a separate group of inventions.**

**However, with regard to the peptabodies, the ISA had grouped the potential inventions by considering the different groups of ligands referred to in claim 10. It is considered that the particular ligand included in the peptabody is responsible for the biological activity of the fusion protein, and therefore, the ligands themselves are considered to be essential technical features necessary for defining each of the potential inventions.**

4. D1 also discloses all the technical features of claim 1 of the present application. D1 discloses 3 isolated and recombinant fusion peptabodies (see figure 2). The peptabodies were expressed in E. coli and the recombinant proteins were purified (see D1, page 752, left column, third paragraph). The peptabodies of D1 comprise:

(a) a portion of the human cartilage oligomer matrix polypeptide (including 48 amino acid residues: see page 749, right column, second paragraph; figure 2; and page 752, left column, third paragraph);

(b) a portion of a hinge (a 17 amino acid peptide: see page 749, right column, second paragraph; figure 2; and page 752, left column, third paragraph) and

(c) an epidermal growth factor receptor ligand (MARSG, MARAKE, or MSRTMS) comprising at least a motif having a three-dimensional structure (see page 752, left column, third paragraph; figure 2; and Table 1). The three peptides included in the peptabodies having the sequences MARSG, MARAKE, and MSRTMS (see figure 2 of D1) comprise the motifs MARSG, MARXX, and MSRTXX respectively (see figure 1 of D1). It is here noted that a hexapeptide has a three-dimensional structure. The fusion peptabody of D1 is capable of inducing cellular death of cancer cells (see figure 6 and page 753, left column, first three paragraphs).

**Thus in the light of the teaching of either D2 or D1, the common concept linking groups 1 to 10 (the subject-matter of claim 1) cannot be regarded as the "single general inventive concept" required by Rule 13 PCT because it is not novel.**

**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING  
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/IB2004/001049

5. The fact that the different inventions have a common broadly defined functional feature (as being an EGFR ligand) is not enough to establish unity of the invention. This is in line with the PCT International Search and Preliminary Examination Guidelines, see section 10.55, example 35. In said section it is stated that "the fact that all fusion proteins have a common property is not sufficient to establish unity of the invention". One of the reasons being because the lack of a common structural element among said fusion proteins.
6. Consequently, the different inventions lacking a common inventive concept were formulated as different subjects (the Applicant's attention is drawn to the fact that the use of the term "invention" here in no way implies recognition of an inventive step for the subject-matter of any group).

A complete search could not be performed with relatively little effort: due to the lack of common technical features independent searches have to be carried out for each of the inventions. The search was initially restricted to the first subject (the first epidermal growth factor receptor ligand mentioned in the claims), and the Applicant was invited to pay additional fees for each additional subject to be searched.
7. **The Applicant elected to pay an additional search fee without protest corresponding to the subject-matter of potential invention 11 (claim 45).**
8. Accordingly, the present opinion relates to inventions 1 and 11, which have been the subject of international search.

**Re Item V**

1. The document numbering corresponds to the order of citation in the search report.

**Lack of clarity**

2. Claim 45 is unclear contravening the requirements of Article 6 PCT, since it refers

**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING  
AUTHORITY (SEPARATE SHEET)**

International application No.

**PCT/IB2004/001049**

to enhancer sequences defined by their activity and sequence, and also to "fragments thereof, a molecular chimera thereof and variants thereof". Said definition ("fragments thereof, a molecular chimera thereof and variants thereof") is vague, rendering the scope of claim 45 unclear. Any enhancer sequence containing one of the amino acids YSFEDLYR would fall under the scope of claim 45.

Furthermore, claim 45 is inconsistent, since even some of the particular peptide sequences recited do not have the claimed effect. As shown in figure 26 of the present application SFEDL (inactive as enhancer) is a fragment of YSFEDL (active as enhancer).

**Lack of novelty**

3. The present application does not meet the criteria of Article 33(1) PCT, because the **subject-matter of claims 1-7, 10-12, 17-23, 25, 27-30, 35, 36, 39 is not new** in the sense of Article 33(2) PCT.

3.1 D2 discloses isolated and recombinant fusion peptabodies expressed in E. coli, which bind to human epidermal growth factor receptor (hEGFR). The peptabodies of D2 comprise:

(a) a portion of the human cartilage oligomer matrix polypeptide (the coiled-coil region);

(b) a portion of a hinge (a semirigid IG hinge region) and

(c) an epidermal growth factor receptor ligand (either hEGF or a biogenic insect peptide of 25 amino acids named growth blocking peptide, GBP, which possesses the ability to interact with EGFR). It is noted that hEGF is very well known to have at least a motif having a three dimensional structure (see e.g. D3, D4, or paragraph bridging pages 8 and 19 of the present application).

The fusion peptabody of D2 is capable of inducing cellular death of cancer cells (see end of the results section).

**Thus, D2 discloses all technical and functional features of claim 1 of the present application.** It is noted that in D2 the fusion proteins are named either peptabody anti EGFR or decabody. As the EGF ligand was bound to the coiled-coil region of the cartilage oligomeric matrix protein which allowed pentamerization of the EGF, and in view of the title, the fusion proteins of D2 are pentabodies.

**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING  
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/IB2004/001049

Furthermore in D2 human EGF was used (which is known to bind to ErbB1), forming a multimeric polypeptide, the hinge was located as claimed in claims 6 and 7, the peptabodies were expressed in *E. coli*, purified, and used to kill cancer cells. Thus D2 is prejudicial to the novelty of claims 1-7, 10, 11, 17-23, 25, 27-30, 35, 36, and 39 of the present application.

3.2 D1 discloses 3 isolated and recombinant fusion peptabodies (see figure 2). The peptabodies were expressed in *E. coli* and the recombinant proteins were purified (see D1, page 752, left column, third paragraph). The peptabodies of D1 comprise:

- (a) a portion of the human cartilage oligomer matrix polypeptide (including 48 amino acid residues: see page 749, right column, second paragraph; figure 2; and page 752, left column, third paragraph);
- (b) a portion of a hinge (a 17 amino acid peptide: see page 749, right column, second paragraph; figure 2; and page 752, left column, third paragraph) and
- (c) an epidermal growth factor receptor ligand (MARSSL, MARAKE, or MSRTMS) comprising at least a motif having a three-dimensional structure (see page 752, left column, third paragraph; figure 2; and Table 1). The three peptides included in the peptabodies having the sequences MARSSL, MARAKE, and MSRTMS (see figure 2 of D1) comprise the motifs MARSSX, MARXXX, and MSRXXX respectively (see figure 1 of D1). It is here noted that a hexapeptide has a three-dimensional structure. The fusion peptabody of D1 is capable of inducing cellular death of cancer cells (see figure 6 and page 753, left column, first three paragraphs).

Furthermore in D1 the peptabody was forming a multimeric polypeptide, the hinge was located as claimed in claims 6 and 7, the peptabody also contains a polyhistidine tag sequence, the peptabodies were expressed in *E. coli*, purified. It is noted that D1 discloses that the 3 anti-ErbB-2 peptabodies inhibited proliferation (or cell growth) of SK-BR-3 cells (see page 753, left column, first three paragraphs, and figure 6). The SK-BR-3 cells are originated from a breast carcinoma cell line from the ATCC (see D1, page 750, right column, second paragraph). SK-BR-3 cells express ErbB-2 (a epidermal growth factor receptor) as disclosed in D1, see page 754, right column, second paragraph). Thus, the peptabodies of D1 were also used to treat cancer cells. D1 is then prejudicial to the novelty of claims 1, 5-7, 11, 12, 17-23, 25, 27-30, 35, 36, and 39.

**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING  
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/IB2004/001049

**Lack of inventive step**

4. Claims 8, 9, 13-16, 24-26, 31-34, 37, 38, and 40-44 do not contain any feature which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of inventive step.
- 4.1 Enhancer peptide sequences were known in the prior art (see abstract of D11 and D12). In D11 the enhancer peptide improves the pharmacokinetic properties of the fusion protein. In D12 the enhancer peptide codes for a transport peptide which is responsible for an enhancement in the production of the protein. Both enhancers are understood to fall under the definition of enhancer in claim 8 of the present application. Thus, the subject-matter of claim 8 is considered as not inventive in view of the teaching of either D1 or D2 combined with the teaching of either D11 or D12, since the skilled person would have been motivated to try to maximize peptide production or to improve the pharmacokinetic properties by using enhancers.
- 4.2 Claim 9 is also not inventive. Some sequences recited in claim 9 do not appear to enhance at all protein production (see for example YSFED on Figure 26 of the present application). If products falling under the scope of a claim do not solve the technical problem posed, the claim as a whole must be considered as not involving an inventive step (see also sections 5 to 5.3 below).
- 4.3 The use of cytotoxin in fusion proteins to be used in methods of treatment was disclosed in D13. The use of fluorescent labels is of standard use in the art. Thus said features is merely one of several straightforward possibilities from which the skilled person would select, in accordance with circumstances, without the exercise of inventive skill, in order to solve the problem posed. Thus, claims 13-16 are also not inventive in view of the teaching of either D1 or D2 combined with the teaching of D13.
- 4.4 The use of the peptabodies of the present application for particular cancers such as head, neck, bladder or melanoma has not been disclosed in the application as filed.

EGF, and EGFRs were known to be expressed in different types of cancer and EGF had been associated with apoptosis (see e.g. D5, page 2; D1; and D2). However, EGF was known to induce and counteract apoptosis depending on the cell type and signalling context (see D5, page 2, or abstract of D15). Thus, if the subject-matter of claims 24, 26, 31-4, 37-38, and 40-44 were not trivial for the skilled person, such

**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING  
AUTHORITY (SEPARATE SHEET)**

International application No.

**PCT/IB2004/001049**

matter would have to be considered as not sufficiently disclosed.

However, EGF was known to induce apoptosis in at least certain cancers such as breast or esophageal cancer (see abstract of D16, or see D2). The skilled person would have tried to use said factors in methods of cancer treatment. Since the polymerization of a given molecule in pentabodies has been shown to be an effective way of enhancing the biological activity of said factor (see, D1, D2, and any of D6 to D10) the skilled person would have tried to use said EGF peptabodies in methods of cancer treatment. The skilled person would have tried to optimize expression conditions and to use adequate carriers. Thus the subject-matter of claims 24, 26, 31-4, 37-38, and 40-44 are also considered as not inventive.

5. The particular peptides mentioned in claim 45 have not been found in the prior art to be disclosed as an enhancer. However **claim 45 is considered not to involve an inventive step** for the following reasons:

- 5.1 The following enhancers have been shown to be active in particular fusion constructs:
- In figure 25 YSFEDL (Enh4) and YSFEDLYRR (Enh8);
  - In figure 26 YSFE (Enh2), and YSFEDL (Enh4).

Other peptides recited in claim 45 do not appear to enhance at all protein production, as for example YSFED (Enh3), SFEDL (Enh5) as disclosed on Figure 26 of the present application).

If products falling under the scope of a claim do not solve the technical problem posed (to provide peptides which enhance protein production), the claim as a whole must be considered as not involving an inventive step.

- 5.2 Furthermore, claim 45 does not only refer to particular peptide enhancers having a defined sequence, but also to "a fragment thereof, a molecular chimera thereof, and variants thereof". However as shown in figure 26 of the present application SFEDL (inactive as enhancer) is a fragment of YSFEDL (active as enhancer). Thus, the claim comprises sequences which do not solve the technical problem and which render the claim not inventive.

- 5.3 It is unclear if the particular peptides referred to in claim <sup>45</sup>~~26~~ are sufficient to enhance

**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING  
AUTHORITY (SEPARATE SHEET)**

International application No.

**PCT/IB2004/001049**

protein production by themselves, or if the claimed function is dependent on the surrounding protein context.

It is possible that the peptides here designated as enhancers could act depending on the particular protein context to function as (part of) a signal peptide. If said enhancers would show the claimed technical effect only in the particular constructs exemplified (and not on any other protein to which they are fused), the isolated peptides would have to be considered as not inventive since they would not provide a technical effect on their own.

6. For the assessment of the present claims 25-31 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The EPO does not recognize as industrially applicable methods of treatment of the human body by surgery or therapy and diagnostic methods practised on the human or animal body. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.